PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
991937WOKB		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/HU00/00049	26/05/2000	10/06/1999
International Patent Classification (IPC) or national classification and IPC C07D327/10		
Applicant RICHTER GEDEON VEGYESZETI GYAR RT. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25/11/2000	12.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Stroeter, T Telephone No. +49 89 2399 8088

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU00/00049

I. Basis f th report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-19 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-16
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-16
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

R It m V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Prior art documents

The following documents (D) were mentioned in the International Search Report and are numbered according to the order of appearance therein. The numbering will be adhered to in the rest of the procedure:

D1: EP-A-0 100 172 (IMPERIAL CHEMICAL INDUSTRIES) 8 February 1984 (1984-02-08) cited in the application

D2: H. TUCKER, ET AL.: 'Nonsteroidal antiandrogens. Synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides' JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 5, 1 May 1988 (1988-05-01), pages 954-959, XP000605264 American Chemical Society, Washington, DEPENDENT CLAIM, US ISSN: 0022-2623 cited in the application

D3: H. TUCKER, ET AL.: 'Resolution of the nonsteroidal antiandrogen 4'-cyano-3-[(4-fluorophenyl)sulphonyl]-2-h ydroxy-2-methyl-3'-(trifluoromethyl)-propi onanilide and the determination of the absolute configuration of the active enantiomer' JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 4, 1 April 1988 (1988-04-01), pages 885-887, XP000605163 American Chemical Society, Washington, DEPENDENT CLAIM, US ISSN: 0022-2623 cited in the application

D1 to D3 reveal i.a. procedures for the preparation of bicalutamide and related antiandrogenic compounds.

2 Novelty (Article 33(2) PCT) and Inventive step (Article 33(3) PCT)

The process as claimed in present **claim 1** (as well as in dependent **claims 2 to 16**) is novel over the processes disclosed in D1 to D3 by showing a different sequence of steps starting from a different starting material.

By revealing such a process, the present application gives a non-obvious solution to the problem of how to provide an alternative process for the preparation of bicalutamide since no indication is given in D1 to D3 that would lead to the present very different synthetic route. Therefore, the claims in question are to be seen as involving an inventive step.

Thus, present claims 1 to 16 are novel and inventive according to Art. 33(2) and Art. 33(3) PCT.

3 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present set of claims 1 to 16 is in accordance with the requirements of Article 33(4) PCT.

Re Item VII

Certain defects in the international application

The Applicant should verify the patent number of cited document WO 93/19770 (page 1, line 20 of the present description). Presumably it is to be changed in WO 95/19770.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
991937WOKB		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/HU 00/ 00049	26/05/2000	10/06/1999
Applicant		
RICHTER GEDEON VEGYESZETI GYAR RT.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the internaticnal application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nuclectide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[ ] contained in the international application in written form.

[ ] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[ ] the text is approved as submitted by the applicant.

[X] the text has been established by this Authority to read as follows:

PROCESS FOR THE SYNTHESIS OF N-(4-CYANO-3-TRIFLUOROMETHYLPHENYL)-3-(4-FLUOROPHENYLSULPHONYL)-2-HYDROXY-2-METHYLPROPIONAMIDE

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 6

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[X] because this figure better characterizes the invention.

[ ] Non of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/HU 00/00049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D327/10 C07C253/30 C07C303/28 C07C309/66 C07C319/14
C07C323/60 C07C315/02 C07C317/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 100 172 A (IMPERIAL CHEMICAL INDUSTRIES) 8 February 1984 (1984-02-08) cited in the application page 27, table, 8th entry claim 6 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2000	27/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

Form PCT/ISA/210 (second sheet) (July 1992)

International Application No
PCT/HU 00/00049

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	H. TUCKER, ET AL.: "Nonsteroidal antiandrogens. Synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 5, 1 May 1988 (1988-05-01), pages 954-959, XP000605264 American Chemical Society, Washington, DC, US ISSN: 0022-2623 cited in the application compound 40 ---	1
A	H. TUCKER, ET AL.: "Resolution of the nonsteroidal antiandrogen 4'-cyano-3-'(4-fluorophenyl)sulphonyl!-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propionanilide and the determination of the absolute configuration of the active enantiomer" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 4, 1 April 1988 (1988-04-01), pages 885-887, XP000605163 American Chemical Society, Washington, DC, US ISSN: 0022-2623 cited in the application the whole document ------	1

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/HU 00/00049

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0100172 A	08-02-1984	AT 28864 T	15-08-1987
		AU 556328 B	30-10-1986
		AU 1693783 A	26-01-1984
		CA 1249823 A	07-02-1989
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		DE 3372965 D	17-09-1987
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		HK 92690 A	16-11-1990
		HU 191296 B	27-02-1987
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		JP 1755775 C	23-04-1993
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		PT 77087 A,B	01-08-1983
		US 4636505 A	13-01-1987
		ZA 8305182 A	30-05-1984

22048

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00608 A1

(51) International Patent Classification[7]: C07D 327/10, C07C 253/30, 303/28, 309/66, 319/14, 323/60, 315/02, 317/46

(21) International Application Number: PCT/HU00/00049

(22) International Filing Date: 26 May 2000 (26.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 9901937 10 June 1999 (10.06.1999) HU

(71) Applicant *(for all designated States except US)*: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.** [HU/HU]; Gyömrői út 19-21, H-1103 Budapest (HU).

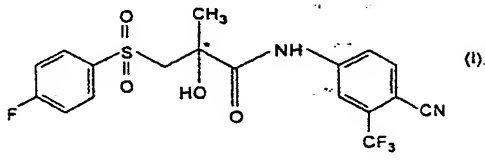
(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **SÖRÖS, Béla** [HU/HU]; Ond vezér út 45, H-1144 Budapest (HU). **TUBA, Zoltán** [HU/HU]; Bogár u. 20/b, H-1022 Budapest (HU). **GÁLIK, György** [HU/HU]; Tüzkő u. 7, H-1118 Budapest (HU). **BOR, Ádám** [HU/HU]; Vöröskő u. 2, H-2040 Budaörs (HU). **DEMETER, Ádám** [HU/HU]; Gyakorló u. 4/f, H-1106 Budapest (HU). **TRISCHLER, Ferenc** [HU/HU]; Úttörő u. 16, H-1171 Budapest (HU). **HORVÁTH, János** [HU/HU]; Cserep u. 7, H-7025 Bölcske (HU). **BRLIK, János** [HU/HU]; Klapka György u. 29, H-1154 Budapest (HU).

(74) Common Representative: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.**; Gyömrői út 19-21, H-1103 Budapest (HU).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

[Continued on next page]

(54) Title: PROCESS FOR THE SYNTHESIS OF N-(4-CYANO-3-TRIFLUOROMETHYLPHENYL)-3-(4-FLUOROPHENYL-SULFONYL)-2-HYDROXY-2-METHYL-PROPIONAMIDE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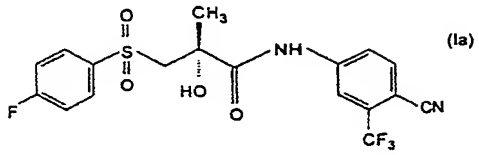
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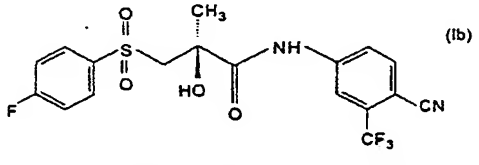

(Ib)

(57) Abstract: The invention relates to a new process for the synthesis of the known racemic and optically pure R-(-)- and S-(+)-N-[4-cyano-3-trifluomethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide of formula (I), (Ia) and (Ib), respectively. The process according to the invention is as follows: the racemic or optically pure 2,3-dihydroxy-2-methyl-propionic acid of formula (VII) is reacted with thionyl chloride in a halogenated hydrocarbon or in an aromatic solvent in the presence of an aromatic amine as base; the obtained racemic or optically pure 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI) is reacted with 4-cyano-3-trifluoromethyl-aniline in an inert solvent in the presence of a tertiary amine as base between 40 and 0 °C; the obtained racemic or optically pure 4-{[4-cyano-3-(trifluoromethyl)-anilino]-carbonyl}-4-methyl-1,3,2-dioxathiolane-2-one of formula (V) is hydrolyzed under aqueous basic conditions; the formed racemic or optically pure N-[4-cyano-3-(trifluoromethyl)-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV) is sulfonylated with a sulfonyl halogenide of formula R-SO_2-X - wherein the meaning of R is methyl, p-tolyl or p-bromo-phenyl group and X represents a halogen atom - in a halogenated hydrocarbon as solvent in the presence of a tertiary amine as base; the obtained racemic or optically pure sulfonic ester derivative of formula (III) - wherein R represents methyl, p-tolyl or p-bromo-phenyl group - is reacted with 4-fluorothiophenol in the presence of a base; finally the obtained racemic or optically pure thioether derivative or formula (II) is oxidized i) with an inorganic peroxy salt in a mixture of water and a solvent miscible or not miscible with water, in the latter case in the presence of a phase transfer catalyst, or ii) with aqueous hydrogen peroxide α) in a C_1-C_4 aliphatic carboxylic acid, or β) under aqueous basic conditions, in given case in the presence of an organic solvent miscible with water, or γ) in an organic solvent not miscible with water in the presence of a phase transfer catalyst and a salt of a metal belonging to the vanadium or chromium group.

WO 01/00608 A1

(84) **Designated States** *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

— *With international search report.*

— *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

CORRECTED VERSION

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number
WO 01/00608 A1

(51) International Patent Classification[7]: C07D 327/10, C07C 253/30, 303/28, 309/66, 319/14, 323/60, 315/02, 317/46

(21) International Application Number: PCT/HU00/00049

(22) International Filing Date: 26 May 2000 (26.05.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
P 9901937 10 June 1999 (10.06.1999) HU

(71) Applicant *(for all designated States except US)*: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.** [HU/HU]; Gyömrői út 19-21, H-1103 Budapest (HU).

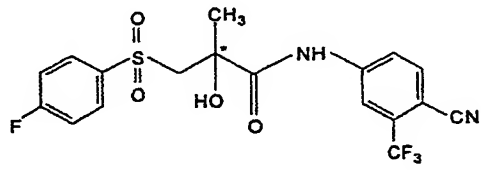
(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SÖRÖS, Béla** [HU/HU]; Ond vezér út 45, H-1144 Budapest (HU). **TUBA, Zoltán** [HU/HU]; Bogár u. 20/b, H-1022 Budapest (HU). **GÁLIK, György** [HU/HU]; Tűzkő u. 7, H-1118 Budapest (HU). **BOR, Ádám** [HU/HU]; Vöröskő u. 2, H-2040 Budaörs (HU). **DEMETER, Ádám** [HU/HU]; Gyakorló u. 4/f, H-1106 Budapest (HU). **TRISCHLER, Ferenc** [HU/HU]; Úttörő u. 16, H-1171 Budapest (HU). **HORVÁTH, János** [HU/HU]; Cserep u. 7, H-7025 Bölcske (HU). **BRLIK, János** [HU/HU]; Klapka György u. 29, H-1154 Budapest (HU).

(74) Common Representative: **RICHTER GEDEON VEGYÉSZETI GYÁR RT.**; Gyömrői út 19-21, H-1103 Budapest (HU).

[Continued on next page]

(54) Title: PROCESS FOR THE SYNTHESIS OF N-(4-CYANO-3-TRIFLUOROMETHYLPHENYL)-3-(4-FLUOROPHENYL-SULFONYL)-2-HYDROXY-2-METHYLPROPIONAMIDE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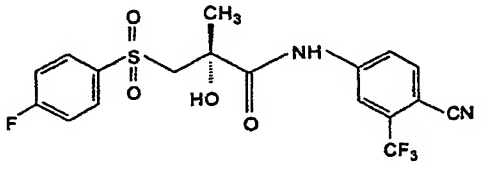
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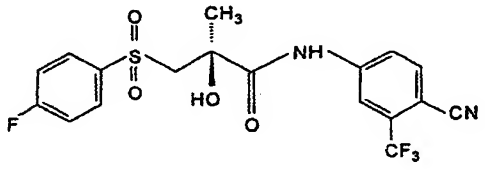
(Ib)

(57) Abstract: Racemic or optically pure N-(4-cyano-3-trifluoromethylphenyl)-3-(4 -fluorophenylsulphonyl)-2-hydroxy-2-methyl-propionamide of formula (I) is prepared by the following process: 2,3-dihydroxy-2-methylpropionic acid of formula (VII) is reacted with thionyl chloride to form 4-chlorocarbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI), which is reacted with 4-cyano-3-trifluoromethylaniline. The resulting 4-{[4-cyano-3-(trifluoromethyl)anilino]carbonyl}-4-methyl-1,3,2-dioxathiolane-2-one of formula (V) is hydrolysed to form N-[4-cyano-3-(trilfuoromethyl)phenyl]-2,3-dihydroxy-2-methylpropionamide of formula (IV), which is sulfonylated with a sulfonyl halogenide of formula R-SO_2-X, in a halogenated hydrocarbon solvent in the presence of a tertiary amine base. The sulphonic ester derivative of formula (III) obtained is reacted with 4-fluorothiophenol in the presence of a base to give a thioether of formula (II) which is oxidized using an inorganic peroxy compound or aqueous hydrogen peroxide.

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PROCESS FOR THE SYNTHESIS OF N-(4-CYANO-3-TRIFLUOROMETHYLPHENYL)-3-(4-FLUOROPHENYL- SULFONYL)-2-HYDROXY-2-METHYL-PROPIONAMIDE

The invention relates to a new process for the synthesis of the known racemic and optically pure R-(-)- and S-(+)-N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide of formula (I), (Ia) and (Ib), respectively. N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide was known as Bicalutamide in therapy.

The racemic and the optically pure Bicalutamide have antiandrogen activity. They decrease the testosterone level selectively in the prostate without influencing the regulation mechanisms of the hypothalamus (the LH-level/testosterone-level negative feedback mechanism). They have higher and more selective biological and clinical activity as compared to Flutamide {2-methyl-N-[4-nitro-3-trifluoromethyl-phenyl]-propionamide}, since they do not increase the testosterone- and the LH-level even at 19 times concentration of ED_{50} in the human body, while the Flutamide doubles them at 3.5 times concentration of ED_{50} [J. Med. Chem., **31**, 954-959 (1988)]. The effect of daily 50 and 150 mg dose was tested in the clinical practice [Proc. Am. Soc. Oncology, **15**, 684 (1996)]. It has been found, that in the case of primary prostate tumors the racemic Bicalutamide combined with an LHRH analog was at least as active as castration, while in the case of secondary tumors it does not substitute that.

The international patent No. WO 93/19770 describes the use of the R-(-) enantiomer. From the two enantiomers the R-(-) isomer was more active. The authors claim, that treatment with the R-(-) isomer was more advantageous, on the one hand because less substance was needed and on the other hand the R-(-) enantiomer was peripherally antiandrogen and therefor its side-effects (headache, gynecomistia, giddiness) were less pronounced, then that of the racemate.

Figure 1, 2 and 3 show the three methods, which were described in EP 100172 patent.

Figure 4 shows an asymmetric synthesis which is given in J. Med. Chem., **31**, 885-887 (1988).

Figure 5 shows the process claimed in present application.

Figure 6 shows the compounds of formulas (I), (Ia) and (Ib).

The synthesis of racemic and optically pure enantiomers of formula (I), (Ia) and (Ib), respectively, was described in the following literature:

The patent No. EP 100172 describes the synthesis of new acylanilids by different known

methods. The description contains the synthesis of compounds of formula (I), (Ia) and (Ib), too.

The methods of Figure 1 and 3 show are described in J. Med. Chem., 31, 954-959 (1988), too.

The separation of the antipodes was described in detail in J. Med. Chem., 31, 885-887 (1988), which was also described in the patent No. EP100172, an asymmetric synthesis was also given, depicted on Figure 4.

According to Figure 1 the starting methacryl acid chloride was reacted with 4-amino-2-trifluoromethyl-benzonitrile in dimethylacetamide at 5°C and the so obtained anilide of formula (1) was refluxed with m-chloroperbenzoic acid (MCPBA on the Figure) in 1,1,1-trichloroethane in the presence of 2,5-di-tert-butyl-methylphenol (this was highly explosive). After the completion of the epoxidation reaction the formed epoxide of formula (2) was isolated. The opening of the epoxide ring of compound of formula (2) was carried out with 4-fluorothiophenol in the presence of sodium hydride, then the obtained thioether derivative of formula (II) was oxidized by known method with m-chloroperbenzoic acid in dichloromethane to yield the final product of formula (I).

According to Figure 2 the starting material was methyl methacrylate, which can be converted into epoxide only under harsh conditions (i.e. with peracetic acid in ethyl acetate at 75°C [J. Am. Chem., 81, 680 (1959)], or with 90% hydrogen peroxide – trifluoroacetic anhydride at 40°C [J. Am. Chem., 77, 89 (1955)], or with MCPBA in dichloromethane at °C in low yield [J. Med. Chem., 29, 2184 (1986)]. The epoxidation under the above mentioned conditions can be explosive. The methyl 2-methyl-oxirane-carboxylate of formula (5), which was obtained by epoxidation, was reacted with 4-fluorothiophenol in the presence of sodium hydride under the conditions given on Figure 1. The obtained methyl 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionate of formula (6) was hydrolyzed with potassium hydroxide in aqueous ethanol over a period of 22 h to yield the 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionic acid of formula (7), which was converted into acid chloride of formula (8) with thionyl chloride in dimethyl acetamide at -15°C. The obtained acid chloride was reacted with 4-amino-2-trifluoromethyl-benzonitrile in dimethylacetamide at -15°C to yield the thioether derivative of formula (II), which was given on Fig. 1. The oxidation of the thioether derivative was carried out according to Fig. 1.

The starting material of the synthesis given on Figure 3 was bromo-acetone, which was reacted according to the literature [Zh. Org. Khim., 7, 2221, (1871)] with 4-fluorothiophenol in the presence of triethylamine, the obtained thioether derivative of formula (9) was reacted with

potassium cyanide under acidic conditions to yield the cyanohydrine derivative of formula (10). The 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionic acid of formula (7) was obtained from the latter by acidic hydrolysis. The 2-hydroxy-2-methyl-3-(4-fluorophenylthio)-propionic acid of formula (7) was converted into acid chloride with thionyl chloride and the latter was transformed into amide and oxidized to yield (±)-Bicalutamide as given above.

Two procedures were known for the synthesis of the optically pure Bicalutamide:

According to one procedure [patent No. EP 100172 and J. Med. Chem., 31, 885-887 (1988)] the thioether derivative of formula (II), which was the key-intermediate of the synthesis of (±)-Bicalutamide, was synthesized, then the resolution was carried out by esterification of the hydroxyl group of the thioether derivative with optically pure R-(-)-camphoric acid chloride, the obtained diastereomers were separated by fractional crystallization or preferably by chromatography, then the optically pure esters were hydrolyzed to yield the corresponding alcohol derivatives and oxidized to give the optically pure Bicalutamide.

According to the other procedure [J. Med. Chem., 31, 885-887 (1988)], which was shown on Figure 4, the optically pure S-(+)-Bicalutamide was obtained by asymmetric synthesis. The starting material of the synthesis was S-(+)-N-methacryloyl-proline of formula (11), which was reacted with N-bromo-succinimide in dimethyl formamide to yield the 3(S)-(bromomethyl)-3(S)-methyl-1,4-dioxo-3,4,6,7,8,8a(S)-hexahydro-1-H-pyrrolo[2,1-c][1,4]-oxazine of formula (12). The latter was hydrolyzed with hydrochloric acid to give the S-(+)-3-bromo-2-hydroxy-2-methyl-propionic acid of formula (13), which was converted into the corresponding acid chloride with thionyl chloride. The acid chloride was reacted with 4-amino-2-trifluoromethyl-benzonitrile to yield the S-(+)-N-{4-cyano-(3-trifluoromethyl)}-3-bromo-2-methyl-2-hydroxy-propion-amide of formula (14). The latter was reacted with 4-fluorothiophenol in the presence of sodium hydride to give the (S)-(+)-N-[4-cyano-3-(trifluoromethyl)-phenyl]-3-[(4-fluorophenyl)-thio]-2-hydroxy-2-methyl-propionamide of formula (15), which was oxidized by known method with m-chloroperbenzoic acid to yield the optically pure S-(+)-Bicalutamide. The R-(-)-Bicalutamide can be synthesized the same way starting from R-(-)-N-methacryloyl-proline.

It was very important to examine a procedure from the point of industrial applicability, whether the procedure fulfils the following requirements:

1) The starting materials of the procedure should be easily available and as cheap as possible.

2) The use of harmful reagents should be avoided during the course of the procedure.

3) The synthesis should be safe from the point of environmental protection.

4) The formation of by-products and ballast materials, which can not be used or processed further, should be minimized during the course of the procedure.

5) The reaction vessels generally used in pharmaceutical and chemical industry should be applicable for the realization of the synthesis.

6) It was very important, that the synthesis should give pure final product, which does not need further, expensive purification.

All of the syntheses described in the literature apply steps, which do not fulfil one or other of the above conditions.

According to Figure 3 the synthesis of cyanohydrine derivative of formula (10) and its further reaction under acidic conditions was dangerous for health. The hydrolysis of the cyanohydrine in the presence of concentrated hydrochloric acid at 110°C or with hydrochloric acid in acetic acid requires special equipment. The use of sodium hydride in tetrahydrofuran was an inflammable step. In the second step (epoxidation) of the first procedure the oxidation was carried out with m-chloroperbenzoic acid. This oxidation step, which was carried out at high temperature (i.e. at 120°C), was explosive.

The known procedures, which were carried out only on few-gram-scale, can lead to further, unexpected problems during the industrial realization. (I.e. an oxidation carried out in a few m^3 reactor can easily 'run over', resulting in an explosion; weighing and adding a large quantity of sodium hydride needs special attention, etc.)

The modern requirements of pharmacopoeia specify numerous analyzing methods, i.e. thin layer or liquid chromatographic content determination, moreover fix and limit the number and the quantity of the impurities, therefor it was a basic requirement, that the product formed during the synthesis should contain the least impurities possible.

Taking into consideration the above mentioned our aim was to elaborate a new, environmental protective, safe, industrially applicable process, which was devoid of the insufficiencies of the known procedures and makes possible the synthesis of both the racemic and the optically pure desired compounds in high yield and was easily realizable industrially.

Surprisingly it was found, that the following process fulfils the above requirements:

the racemic or optically pure 2,3-dihydroxy-2-methyl-propionic acid of formula (VII) was reacted with thionyl chloride in a halogenated hydrocarbon or in an aromatic solvent in the presence of an aromatic amine as base,

the obtained racemic or optically pure 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI) was reacted with 4-cyano-3-trifluoromethyl-aniline in an inert solvent in the presence of a tertiary amine as base between–40 and 0°C,

the obtained racemic or optically pure 4-{[4-cyano-3-(trifluoromethyl)-anilino]-carbonyl}-4-methyl-1,3,2-dioxathiolane-2-one of formula (V) was hydrolyzed under aqueous basic conditions,

the formed racemic or optically pure N-[4-cyano-3-(trifluoromethyl)-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV) was sulfonylated with a sulfonyl halogenide of formula $R\text{-}SO_2\text{-}X$ – wherein the meaning of R was methyl, p-tolyl or p-bromo-phenyl group and X represents a halogen atom – in a halogenated hydrocarbon as solvent in the presence of a tertiary amine as base,

the obtained racemic or optically pure sulfonic ester derivative of formula (III) – wherein R represents methyl, p-tolyl or p-bromo-phenyl group – was reacted with 4-fluorothiophenol in the presence of a base,

finally the obtained racemic or optically pure thioether derivative of formula (II) was oxidized

i) with an inorganic peroxy salt in a mixture of water and a solvent miscible or not miscible with water, in the latter case in the presence of a phase transfer catalyst, or

ii) with aqueous hydrogen peroxide

α) in a C_1-C_4 aliphatic carboxylic acid, or

β) under aqueous basic conditions, in given case in the presence of an organic solvent miscible with water, or

γ) in an organic solvent not miscible with water in the presence of a phase transfer catalyst and a salt of a metal belonging to the vanadium or chromium group.

The process according to our invention was illustrated on Figure 5, the individual reaction steps were preferably carried out the following way:

The starting material, the 2,3-dihydroxy-2-methyl-propionic acid of formula (VII), was prepared from the commercially available methacrylic acid by oxidation with 40% aqueous hydrogen peroxide in the presence of tungstic acid catalyst.

If the starting material was the racemic 2,3-dihydroxy-2-methyl-propionic acid of formula (VII), then the racemic final product was obtained via racemic intermediates. If one of the optically pure antipode of 2,3-dihydroxy-2-methyl-propionic acid of formula (VII) was used as

starting material in the above process, then the intermediates were optically pure compounds and the last oxidation step results in one of the optically pure antipode of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide. Since the further reaction steps of our invention can be carried out under the same reaction conditions for both the racemic both the optically pure enantiomers giving the same yield, we do not mention the optical purity of the chiral intermediates and the products in the following description. (The synthesis of the optically pure enantiomers of 2,3-dihydroxy-2-methyl-propionic acid was described in detail in the experimental part.)

The above given steps of the process according to our invention were described in detail as follows:

The 2,3-dihydroxy-2-methyl-propionic acid of formula (VII) was reacted with thionyl chloride preferably in toluene solution in the presence of pyridine as aromatic amine. After completion of the reaction the obtained 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI) was purified in given case by distillation.

In the next step of the reaction sequence the dioxathiolane derivative of formula (VI) was reacted with 4-cyano-3-trifluoromethyl-aniline in the presence of triethylamine as tertiary base between –40 and 0°C, preferably between –20 and -10°C, then after completion of the reaction the formed amide of formula (V) was isolated. The opening of the dioxathiolane ring was carried out in a mixture of water and a solvent miscible with water, preferably in aqueous tetrahydrofuran, under basic conditions, preferably in the presence of an aqueous alkali metal hydroxide solution.

The N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV) obtained in the opening reaction of the dioxathiolane ring was reacted with methanesulfonyl chloride or p-toluenesulfonyl chloride or p-bromo-benzenesulfonyl chloride in a halogenated solvent, preferably in dichloromethane, in the presence of a tertiary amine as base, preferably pyridine, between –10 and +10°C, preferably at 0°C, then after completion of the reaction the obtained sulfonyl ester derivative of formula (III) – wherein the meaning of R was methyl, p-tolyl or 4-bromophenyl group – was isolated.

The obtained sulfonyl ester derivative of formula (III) – using the advantage, that the sulfonyl group was a good leaving group – was reacted with 4-fluorothiophenol in an inert atmosphere in isopropanol as solvent in the presence of an inorganic base, i.e. sodium or potassium hydroxide, preferably sodium hydroxide. After completion of the reaction the pH of

the reaction mixture was adjusted to neutral, the solution was treated with charcoal, filtered and made basic again to remove the excess of 4-fluorothiophenol. The precipitated crystals were filtered off, washed neutral and dried.

According to our invention the obtained thioether derivative of formula (II) can be oxidized to Bicalutamide by several oxidizing agents. So the thioether derivative of formula (II) can be oxidized with an inorganic peroxy salt, preferably with a combination of potassium hydrogenpersulfate/potassium hydrogensulfate/potassium sulfate known as Oxone®, in a mixture of water and a solvent miscible with water or not miscible with water. If the used solvent was not miscible with water, then a phase transfer catalyst was used to increase the speed of the reaction. The used solvent miscible with water was preferably a C_1-C_4 alkanole and the solvent not miscible with water was an ester or a halogenated hydrocarbon. As alkanole preferably methanol was used, while as ester type solvent preferably ethyl acetate was used. As halogenated solvent dichloromethane can be used in the oxidation reaction.

As oxidizing agent concentrated aqueous hydrogen peroxide solution can also be used. In this case the thioether derivative of formula (II) was dissolved in a C_1-C_4 aliphatic carboxylic acid and the aqueous hydrogen peroxide solution was added to this. The aliphatic carboxylic acid was preferably formic acid or acetic acid. The thioether derivative of formula (II) can also be oxidized under aqueous basic conditions with hydrogen peroxide. In this case a solvent miscible with water can also be used. An aqueous solution of an alkali metal carbonate was preferably used as basic medium and acetonitrile or C_1-C_4 alkanole, preferably methanol was used as solvent miscible with water.

According to our invention the oxidation with aqueous hydrogen peroxide solution can also be carried out in a solvent not miscible with water in the presence of a phase transfer catalyst and a salt of a metal belonging to the vanadium or chromium group. In this case a halogenated solvent, preferably dichloromethane was used as solvent not miscible with water and sodium tungstate or ammonium molybdate was used as a salt of a metal belonging to the vanadium or chromium group. In this case a phase transfer catalyst was used to increase the speed of the reaction.

A tetraalkyl ammonium salt was preferably used as phase transfer catalyst in the oxidation step of our invention, not limiting examples: tetrabutylammonium chloride and hydrogensulfate or cetyltrimethylammonium chloride and hydrogensulfate.

In the above oxidation steps an adduct of hydrogen peroxide and urea, dimethyl

dioxirane, potassium hydrogenpersulfate or hydrogen peroxide / ammonium molybdate can also be used instead of aqueous hydrogen peroxide.

Several of the intermediates of the invention were new compounds. Such as the (+)-2,3-dihydroxy-2-methyl-propionic acid sodium salt and the (-)-2,3-dihydroxy-2-methyl-propionic acid sodium salt of formula (VII)

the (±)-4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one and the optically pure (+)-4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one and (-)-4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI)

the (±)-N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide and the optically pure (+)-N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propion-amide and (-)-N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV)

(±)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-2-methanesulfonyl-oxy-2-methyl-propionamide and the optically pure (+)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-2-methanesulfonyloxy-2-methyl-propion-amide and (-)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-2-methane-sulfonyloxy-2-methyl-propionamide, the (±)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-methylphenyl-sulfonyloxy]-2-methyl-propionamide and the optically pure (+)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-methylphenyl-sulfonyloxy]-2-methyl-propionamide and (-)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-methyl-phenyl-sulfonyloxy]-2-methyl-propionamide, the (±)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-bromophenyl-sulfonyloxy]-2-methyl-propionamide and the optically pure (+)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-bromophenyl-sulfonyl-oxy]-2-methyl-propionamide and (-)-N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-bromophenyl-sulfonyloxy]-2-methyl-propion-amide of formula (III).

The starting material of the last step of the synthesis and the final product were known, but our invention describes a new process for the synthesis of the latter – and for the synthesis of the new compounds as well - as mentioned above.

The process according to our invention not only solves the synthesis of the final product partly via new compounds, but fulfils the economical and environmental protective requirements of an industrial synthesis as well. The advantages of our process were the following:

1) The starting material of the synthesis was easily available and cheap.

2) The starting material makes possible the synthesis of such intermediates, which were

suitable for the synthesis of the pure enantiomers of the final product.

3) The reaction conditions of the oxidation steps were safe and can be carried out without environmental pollution.

4) The use of inflammable sodium hydride can be avoided during the course of the synthesis.

5) Our process does not use reagents, which were especially harmful for health, i.e. potassium cyanide in acidic medium.

6) The industrial realization of our process does not need special equipment – in contrast to the known procedure (i.e. acid and pressure resistant autoclave for the hydrolysis of the cyanohydrine in concentrated hydrochloric acid at 110°C).

7) The products were obtained pure enough, so their further purification can be solved with simple purification methods, the chromatography can be avoided.

8) The procedures known from the literature describe the synthesis of optically active Bicalutamide either by resolution of the racemic compound of formula (II), which was the last intermediate of the synthesis, and oxidation of the resolved intermediate or by asymmetric synthesis from S-(-)-methacryloyl-proline, which was not easily available and expensive starting material. In the previous case half of the synthesized compound of formula (II) – the unwanted enantiomer – was lost, while in the second case the starting material of the synthesis was hardly accessible.

The process according to our invention was illustrated in detail by the following not limiting examples.

Example 1

Racemic and optically pure 2,3-dihydroxy-2-methyl-propionic acid

a) The synthesis of racemic 2,3-dihydroxy-2-methyl-propionic acid:

A mixture of 76.0 g of water, 51.0 g of 40% aqueous hydrogen peroxide and 1.0 g of tungstic acid was stirred at 55-60°C for 1 h, then the so obtained pertungstic acid - hydrogen peroxide reagent was cooled to 30-35°C. A solution of 33.9 ml (0.4 mol) of methacrylic acid and 0.66 g (6.0 mmol) of hydroquinone in 70 g of water was added to the pertungstic acid - hydrogen peroxide reagent. After the addition the reaction mixture was stirred at 60°C for 7 h, then it was extracted twice with 50 ml of ethyl acetate. A suspension of 0.1 g of palladium on charcoal catalyst and 5 g of water was added to the water phase and the mixture was stirred at 70-72°C for 1 h. The catalyst was filtered off, the filtrate was concentrated in vacuum and the residue was

recrystallized from acetonitrile to yield 30.3-31.2 g (63.1-65%) of the racemic title compound.

b) The synthesis of R-(-)-2,3-dihydroxy-2-methyl-propionic acid:

12.01 g (0.1 mol) of racemic 2,3-dihydroxy-2-methyl-propionic acid was refluxed in 60 ml of acetone until the solid material was dissolved, then the heating was stopped and 14.27 g (0.05 mol) of (+)-dehydro-abiethylamine in 14 ml of acetone was added. After the addition crystal seeds of pure R-(-)-2,3-dihydroxy-2-methyl-propionic acid – (+)-dehydro-abiethylamine salt was added. The mixture was cooled to -5°C and stirred at this temperature for 30 min. The precipitated crystals were filtered off, washed with 12 ml of acetone cooled to -5°C and dried to yield 15.1 g of crude R-(-)-2,3-dihydroxy-2-methyl-propionic acid – (+)-dehydro-abiethylamine salt. Mp: 170-180°C. (The mother liquor obtained in the resolution was concentrated in vacuum and the obtained 11.3 g of residue was used for the resolution of the S-(+)-antipode.)

The obtained 15 g of crude R-(-)-2,3-dihydroxy-2-methyl-propionic acid – (+)-dehydro-abiethylamine salt was dissolved in dry ethanol, the solution was cooled to -5°C and stirred at this temperature for 30 min. the precipitated crystals were filtered off washed with 8 ml of dry ethanol cooled to -5°C and dried to yield 6.6 g of pure R-(-)-2,3-dihydroxy-2-methyl-propionic acid – (+)-dehydro-abiethylamine salt as white, crystalline compound. Mp: 196-197°C. $[\alpha]_D$ = +22.6° (c=1, ethanol). $[\alpha]_{365}$ = +75.9° (c=1, ethanol). (The mother liquor obtained in the recrystallization was concentrated in vacuum and the obtained 8.4 g of residue was used for the resolution of the S-(+)-antipode.)

6.5 g of R-(-)-2,3-dihydroxy-2-methyl-propionic acid – (+)-dehydro-abiethylamine salt was suspended in 13 ml of water and a calculated amount of 10% aqueous sodium hydroxide solution was added. Then 20 ml of chloroform was added to the reaction mixture vigorously stirred then let them separate. After the separation of the phases the pH of the water phase was checked and in given case adjusted to 12. Then the phases were separated, the water phase was extracted three times with 20 ml of chloroform, then concentrated in vacuum to yield 2.2 g of optically pure R-(-)-2,3-dihydroxy-2-methyl-propionic acid sodium salt as white, crystalline powder. Mp: 178-179°C. $[\alpha]_D$ = -3.6° (c=1, water). $[\alpha]_{365}$ = -13.1° (c=1, water).

5 g of R-(-)-2,3-dihydroxy-2-methyl-propionic acid sodium salt was dissolved in 5 ml of water and 15 g of 10% aqueous hydrochloric acid was added. The so obtained aqueous solution was concentrated under diminished pressure and twice 10 ml of acetonitrile was distilled off from the residue. The resiodue was dissolved in 25 ml of acetonitrile, the precipitated sodium chloride was filtered off and washed twice with 5 ml of acetonitrile. The combined acetonitrile

phase was concentrated under diminished pressure to yield 4.22 g of R-(-)-2,3-dihydroxy-2-methyl-propionic acid. . Mp: 68-70°C. $[\alpha]_D$ = -2.6° (c=1, water). $[\alpha]_{365}$ = -6.1° (c=1, water).

The residues collected for the resolution of the S-(+)-antipode were combined, the so obtained 19.7 g material was dissolved in 40 ml of ion-exchanged water 20 ml of chloroform was added and the pH of the stirred mixture was adjusted to 12 by adding 10% aqueous sodium hydroxide solution. After separation of the phases the water phase was extracted three times with 20 ml of chloroform. This chloroform solution was combined with chloroform solutions obtained during the preparation of R-(-)-2,3-dihydroxy-2-methyl-propionic acid sodium salt, dried over sodium sulfate and concentrated to yield 13.85 g of S-(+)-2,3-dihydroxy-2-methyl-propionic acid.

The water phase obtained above was acidified with 3 M aqueous hydrochloric acid to pH = 2 and concentrated in vacuum. 50 ml of acetone was added to the residue and the 2,3-dihydroxy-2-methyl-propionic acid was dissolved from beside the sodium chloride. The acetone solution was concentrated, 8 ml of acetonitrile and subsequently seeds of 2,3-dihydroxy-2-methyl-propionic acid were added, the mixture was cooled to 0°C and stirred at this temperature for 30 min. The precipitated 2,3-dihydroxy-2-methyl-propionic acid was filtered off, washed twice with 4 ml of acetonitrile cooled to 0°C and dried to yield 8.15 g of racemic 2,3-dihydroxy-2-methyl-propionic acid, which has the S-(+)-antipode as impurity. Mp: 95-100°C.

Concentration of the acetonitrile solution yields further 1.65 g of optically pure S-(+)-2,3-dihydroxy-2-methyl-propionic acid.

Example 2

4-Chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one

A mixture of 75 g (0.624 mol) of 2,3-dihydroxy-2-methyl-propionic acid, 2000 ml of toluene and 1.5 ml of pyridine was cooled to 10°C and 112.5 ml (1.524 mol) of thionyl chloride was added. After the addition the mixture was refluxed for 4 h, then concentrated under diminished pressure and the residue was distilled in vacuum. The boiling point of the title compound was 62°C at 6.5 mbar. The optically pure isomers were synthesized analogously.

Title compound	Yield [g]	Yield [%]	Boiling point at 6.5 mbar [°C]
racemate	90.0	78.0	62
R-(-)	86.5	75.0	62
S-(+)	83.1	72.0	62

Example 3

N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide

To a solution of 44 g (0.236 mol) of 4-cyano-3-trifluoromethyl-aniline in 880 ml of dichloromethane 90 ml of triethylamine was added and the reaction mixture was cooled to -15°C. 64 ml (0.49 mol) of 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one was added dropwise at this temperature. The reaction mixture was stirred at 0°C for 3 h, then extracted with 500 ml of 10% hydrochloric acid solution, the organic layer was dried over sodium sulfate and concentrated under diminished pressure. The residue was dissolved in 1 l of tetrahydrofuran and 440 ml of 10% sodium hydroxide solution was added at 10°C with cooling. The mixture was stirred for 30 min, then the pH was adjusted to 2 by adding 88 ml of concentrated hydrochloric acid and the solution was evaporated to a volume of 100 ml. The residue was dissolved in 260 ml of ethyl acetate, treated with charcoal, filtered and 520 ml of petroleum ether was added to the filtrate. The precipitated crystals were filtered off and dried at 60°C in vacuum. The compounds below were synthesized analogously, using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	46.64	68.5	107-108	-
R-(-)	55.87	82.0	130-131	-43.6
S-(+)	55.87	82.0	132-133	+43.2

Example 4

N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-methanesulfonyloxy-2-methyl-propionamide

A solution of 46 g (0.16 mol) of N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide in 1 l of dichloromethane and 46 ml (0.57 mol) of dry pyridine was cooled to 0°C and 46 ml (0.59 mol) of methanesulfonyl chloride was added dropwise. The mixture was stirred at 0°C for 5 h, then washed three times with 500 ml of saturated aqueous sodium hydrogen carbonate, 500 ml of 10% aqueous hydrochloric acid and 500 ml of brine. The organic layer was dried over sodium sulfate and concentrated in vacuum. The residue was crystallized with 200 ml of petroleum ether, which has a boiling range of 40-70°C.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	49.70	85	119-120	-
R-(-)	52.62	90	106-107	-43.1
S-(+)	52.62	90	118-119	+43.1

Example 5

N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-methylphenyl-sulfonyloxy]-2-methyl-propionamide

A solution of 5 g (17.35 mmol) of N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide in 50 ml of dry pyridine was cooled to 0°C and 10 g (52.45 mmol) of p-toluenesulfonyl chloride was added in small portions. The mixture was stirred at 0°C for 5 h, then diluted with 200 ml of dichloromethane, washed three times with 50 ml of saturated aqueous sodium hydrogen carbonate, twice with 50 ml of 10% aqueous hydrochloric acid and 50 ml of brine. The organic layer was dried over sodium sulfate and concentrated in vacuum. The residue was crystallized from a 1:5 mixture of ethyl acetate / petroleum ether, which has a boiling range of 40-70°C.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	6.80	85	140-141	-
R-(-)	6.52	82	125-126	-42.9
S-(+)	6.52	82	125-127	+42.6

Example 6

N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-[4-bromophenyl-sulfonyloxy]-2-methyl-propionamide

A solution of 5 g (17.35 mmol) of N-[4-cyano-3-trifluoromethyl-phenyl]-2,3-dihydroxy-2-methyl-propionamide in 50 ml of dry pyridine was cooled to 0°C and 8.86 g (34.70 mmol) of 4-bromo-benzenesulfonyl chloride was added in small portions. The mixture was stirred at 0°C for 5 h, then diluted with 200 ml of dichloromethane, washed three times with 50 ml of saturated aqueous sodium hydrogencarbonate, twice with 50 ml of 10% aqueous hydrochloric acid and 50 ml of brine. The organic layer was dried over sodium sulfate and concentrated in vacuum. The residue was crystallized from a 1:5 mixture of ethyl acetate / petroleum ether, which has a boiling range of 40-70°C.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	6.60	75	135-137	-
R-(-)	6.86	78	122-124	-44.4
S-(+)	6.60	75	123-124	+44.2

Example 7

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-thio]-2-hydroxy-2-methyl-propionamide

Under nitrogen, to a solution of 25.6 g (0.20 mol) of 4-fluorthiophenol in 500 ml of isopropanol 8.4 g (0.20 mol) of sodium hydroxide in 400 ml of water was added. The mixture was stirred at 25 °C for 2 h, then 58.6 g (16 mmol) of N-[4-cyano-3-trifluoromethyl-phenyl]-2-hydroxy-3-(methanesulfonyloxy)-2-methyl-propionamide in 500 ml of isopropanol was added. Then the mixture was stirred at 25°C for 5 h, then the pH was adjusted to neutral with concentrated hydrochloric acid and treated with charcoal at reflux temperature. Most of the isopropanol was evaporated in vacuum and 250 ml of 2% aqueous sodium hydroxide solution was added to the residue under vigorous stirring, then the crystalline mixture was left for 1 h, then filtered and washed with water. The dried crystals were recrystallized from a 1:4 mixture of ethyl acetate / petroleum ether, which has a boiling range of 40-70°C.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	52.88	83	116-118	-
R-(-)	54.80	86	97-98	-2.80
S-(+)	52.88	83	96-97	+2.68

Example 8

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

A solution of 52 g (0.13 mol) of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-thio]-2-hydroxy-2-methyl-propionamide in 520 ml of acetic acid was cooled to 10°C and 156 ml of 30% aqueous hydrogen peroxide solution was added. The reaction mixture was stirred overnight, then poured into 3 l of saturated aqueous sodium hydrogencarbonate and extracted three times with 500 ml of dichloromethane, then the combined organic layers were washed with 500 ml of brine, dried over sodium sulfate and concentrated under diminished pressure. The residue was dissolved in 500 ml of ethyl acetate, cooled to +5°C and 2000 ml of petroleum ether, which has a boiling range of 40-70°C, was added. The precipitated crystals were filtered off, washed with 40 ml of petroleum ether cooled to 0°C and dried at 60°C in vacuum.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	47.25	84.15	191-193	-
R-(-)	47.66	84.88	181-182	-80.04
S-(+)	46.14	82.17	180-181	+79.7

Example 9

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

The reaction was carried out as described in Example 8, with the difference that 520 ml of

formic acid was used instead of acetic acid.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	45.01	80.15	-
R-(-)	46.20	82.28	-80.12
S-(+)	43.64	77.71	+79.83

Example 10

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

To a solution of 2 g (2.51 mmol) of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-thio]-2-hydroxy-2-methyl-propionamide in 10 ml of acetonitrile, 20 ml of methanol and 0.6 ml of water 0.38 g (2.75 mmol) of potassium carbonate was added. The mixture was cooled to 5°C and 10 ml of 30% aqueous hydrogen peroxide solution was added dropwise. The mixture was stirred at 25°C overnight, then diluted with 100 ml of water and extracted twice with 100 ml of dichloromethane. The organic layer was washed with 50 ml of brine, dried over sodium sulfate and concentrated under diminished pressure. The residue was recrystallized from a 1:4 mixture of ethyl acetate / petroleum ether, which has a boiling range of 40-70°C. The yield was 1.53 g (70.83%).

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	1.53	70-83	191-193	-
R-(-)	1.59	73.61	181-182	-80.20
S-(+)	1.46	67.59	179-180	+79.92

Example 11

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

To a solution of 2 g (2.51 mmol) of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-thio]-2-hydroxy-2-methyl-propionamide in 20 ml of dichloromethane 5 mg of sodium tungstate and 5 mg of tetrabutylammonium hydrogensulfate phase transfer catalyst were added. 8 ml of 30% aqueous hydrogen peroxide solution was added dropwise to the mixture at room temperature and it was stirred for 8 h at this temperature. The phases were separated, the organic phase was washed twice with 20 ml of 10% aqueous sodium thiosulfate solution, then with brine, dried over sodium sulfate and concentrated under diminished pressure. The residue was recrystallized from a 1:4 mixture of ethyl acetate / petroleum ether, which has a boiling range of 40-70°C.

The same quantity of tetrabutylammonium chloride or cetyltrimethyl-ammonium chloride can also be used resulting in the same yield. The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	1.68	77.80	191-193	-
R-(-)	1.66	76.85	181-182	-80.5
S-(+)	1.63	75.46	180-181	+79.98

Example 12

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

To a solution of 40 g (0.1 mol) of N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-thio]-2-hydroxy-2-methyl-propionamide in 600 ml of methanol and 400 ml of water 100 g (0.16 mol) of Oxone® oxidizing agent [$2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ salt] was added. The reaction mixture was stirred at 25°C for 6 h, then the methanol was distilled off under diminished pressure and the residue was extracted twice with 500 ml of dichloromethane. The organic layer was washed twice with 400 ml of 10% aqueous sodium thiosulfate solution, then with brine, dried over sodium sulfate and concentrated under diminished pressure. The residue was recrystallized from a 1:4 mixture of ethyl acetate / petroleum ether, which has a boiling

range of 40-70°C. The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	36.00	83.33	191-193	-
R-(-)	37.12	85.93	181-182	-80.15
S-(+)	37.01	85.67	180-181	+79.96

Example 13

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

The reaction was carried as described in Example 12, with the difference that 600 ml of dichloromethane was used instead of 600 ml of methanol and 0.5 g of tetrabutylammonium hydrogensulfate was used as phase transfer catalyst. The N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide was isolated from the dichloromethane solution as described in Example 12.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	34.12	78.98	191-193	-
R-(-)	34.55	79.97	181-182	-80.10
S-(+)	33.71	78.03	180-181	+79.89

Example 14

N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide

The reaction was carried as described in Example 12, with the difference that 600 ml of ethyl acetate was used instead of 600 ml of methanol and 0.5 g of tetrabutylammonium hydrogensulfate was used as phase transfer catalyst. The N-[4-cyano-3-trifluoromethyl-phenyl]-

3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide was isolated from the ethyl acetate solution as described in Example 12.

The following compounds were synthesized analogously using the same quantity of the starting material:

Title compound	Yield [g]	Yield [%]	Melting point [°C]	$[\alpha]_D^{22}$ [°] (c=1, methanol)
racemate	36.77	85.12	191-193	-
R-(-)	37.11	85.90	181-182	-80.16
S-(+)	36.16	83.71	180-181	+79.91

What we claim is:

1. A new process for the synthesis of the racemic and optically pure R-(-)- and S-(+)-N-[4-cyano-3-trifluoromethyl-phenyl]-3-[4-fluorophenyl-sulfonyl]-2-hydroxy-2-methyl-propionamide of formula (I), (Ia) and (Ib), respectively, characterized by

reacting the racemic or optically pure 2,3-dihydroxy-2-methyl-propionic acid of formula (VII) with thionyl chloride in a halogenated hydrocarbon or in an aromatic solvent in the presence of an aromatic amine as base,

reacting the obtained racemic or optically pure 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI) with 4-cyano-3-trifluoromethyl-aniline in an inert solvent in the presence of a tertiary amine as base between –40 and 0°C,

hydrolyzing the obtained racemic or optically pure 4-{[4-cyano-3-(trifluoromethyl)-anilino]-carbonyl}-4-methyl-1,3,2-dioxathiolane-2-one of formula (V) under aqueous basic conditions,

sulfonylating the formed racemic or optically pure N-[4-cyano-3-(trifluoromethyl)-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV) with a sulfonyl halogenide of formula R-SO_2-X – wherein the meaning of R was methyl, p-tolyl or p-bromo-phenyl group and X represents a halogen atom – in a halogenated hydrocarbon as solvent in the presence of a tertiary amine as base,

reacting the obtained racemic or optically pure sulfonic ester derivative of formula (III) – wherein R represents methyl, p-tolyl or p-bromo-phenyl group –with 4-fluorothiophenol in the presence of a base,

finally oxidizing the obtained racemic or optically pure thioether derivative of formula (II)

i) with an inorganic peroxy salt in a mixture of water and a solvent miscible or not miscible with water, in the latter case in the presence of a phase transfer catalyst, or

ii) with aqueous hydrogen peroxide

α) in a C_1-C_4 aliphatic carboxylic acid, or

β) under aqueous basic conditions, in given case in the presence of an organic solvent miscible with water, or

γ) in an organic solvent not miscible with water in the presence of a phase transfer catalyst and a salt of a metal belonging to the vanadium or chromium group.

2) The process in claim 1, characterized by carrying out the reaction of the racemic or

optically pure 2,3-dihydroxy-2-methyl-propionic acid with thionyl chloride in dichloromethane, chloroform or 1,2-dichloroethane as halogenated hydrocarbon, or in benzene, toluene or xylene as aromatic solvent in the presence of pyridine as aromatic base.

3) The process in claim 1, characterized by reacting the racemic or optically pure 4-chloro-carbonyl-4-methyl-1,3,2-dioxathiolane-2-one of formula (VI) with 4-cyano-3-trifluoromethyl-aniline in the presence of triethylamine as tertiary amine base.

4) The process in claim 3, characterized by using a halogenated or an aromatic hydrocarbon or an ether type solvent as inert solvent.

5) The process in claim 3, characterized by carrying out the reaction between –15 and 0°C.

6) The process in claim 1, characterized by carrying out the hydrolysis of the racemic or optically pure 4-{[4-cyano-3-(trifluoromethyl)-anilino]-carbonyl}-4-methyl-1,3,2-dioxathiolane-2-one of formula (V) in aqueous medium containing an alkali metal hydroxide.

7) The process in claim 1, characterized by sulfonylating the racemic or optically pure N-[4-cyano-3-(trifluoromethyl)-phenyl]-2,3-dihydroxy-2-methyl-propionamide of formula (IV) with a sulfonyl halogenide of formula $R\text{-}SO_2\text{-}X$ – wherein the meaning of R was as mentioned in claim 1 – in dichloromethane as halogenated hydrocarbon solvent in the presence of pyridine as tertiary amine base.

8) The process in claim 1, characterized by reacting the racemic or optically pure sulfonic ester derivative of formula (III) – wherein the meaning of R was as mentioned in claim 1 –with 4-fluorothiophenol in the presence of an inorganic base, preferably sodium hydroxide as base in isopropanol solution.

9) The process in claim 1, characterized by oxidizing the racemic or optically pure thioether derivative of formula (II) with a mixture of $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Oxone®) as inorganic peroxy salt.

10) The process in claim 9, characterized by carrying out the oxidation in a mixture of methanol and water.

11) The process in claim 9, characterized by carrying out the oxidation in a mixture of dichloromethane and water in the presence of a phase transfer catalyst.

12) The process in claim 9, characterized by carrying out the oxidation in a mixture of ethyl acetate and water in the presence of a phase transfer catalyst.

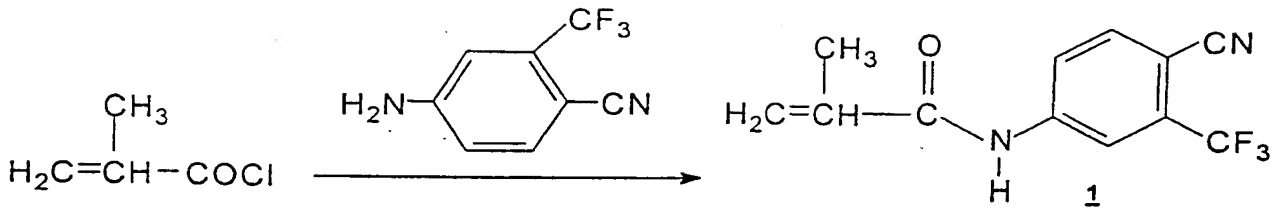
13) The process in claim 1, characterized by carrying out the oxidation of the racemic or

optically pure thioether derivative of formula (II) in formic acid or acetic acid as C_1-C_4 aliphatic carboxylic acid in the presence of aqueous hydrogen peroxide.

14) The process in claim 1, characterized by carrying out the oxidation of the racemic or optically pure thioether derivative of formula (II) in aqueous alkali metal carbonate solution as aqueous basic medium, in given case in the presence of acetonitrile and/or a C_1-C_4 alkanol, preferably methanol as solvent miscible with water in the presence of aqueous hydrogen peroxide.

15) The process in claim 1, characterized by carrying out the oxidation of the racemic or optically pure thioether derivative of formula (II) in a halogenated hydrocarbon, preferably in dichloromethane as organic solvent not miscible with water in the presence of a quaternary ammonium salt as phase transfer catalyst and sodium tungstate with aqueous hydrogen peroxide.

16) The process in claim 11, 12 and 15, characterized by using tetrabutyl-ammonium hydrogensulfate, cetyltrimetylammonium chloride or tetrabutyl-ammonium chloride as phase transfer catalyst.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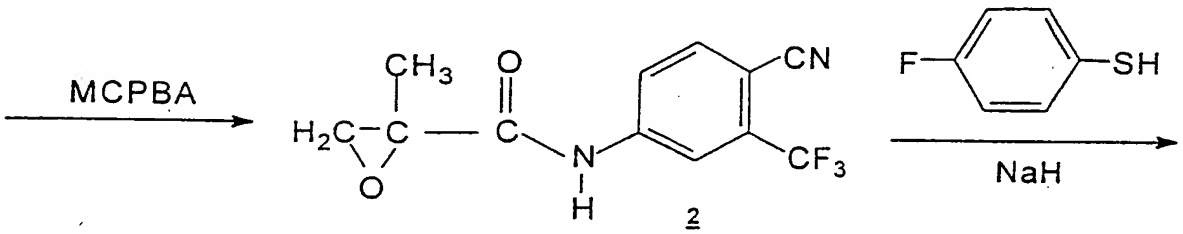
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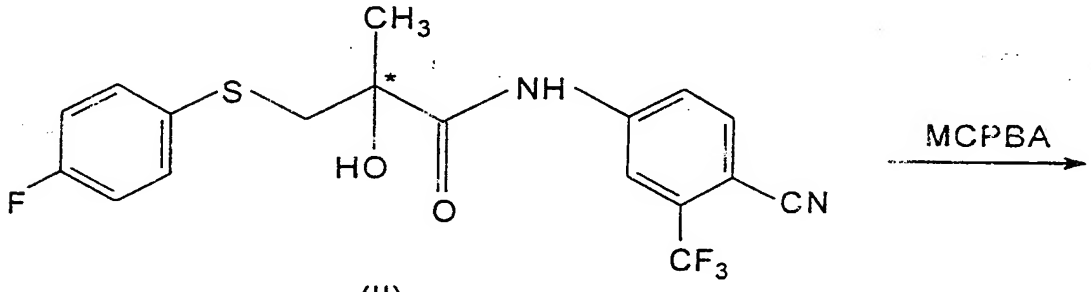
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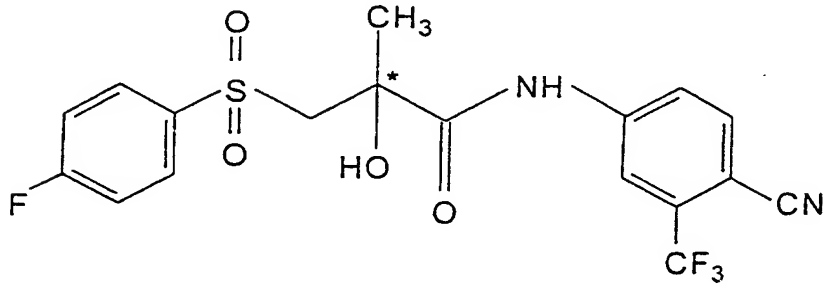
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Fig. 1

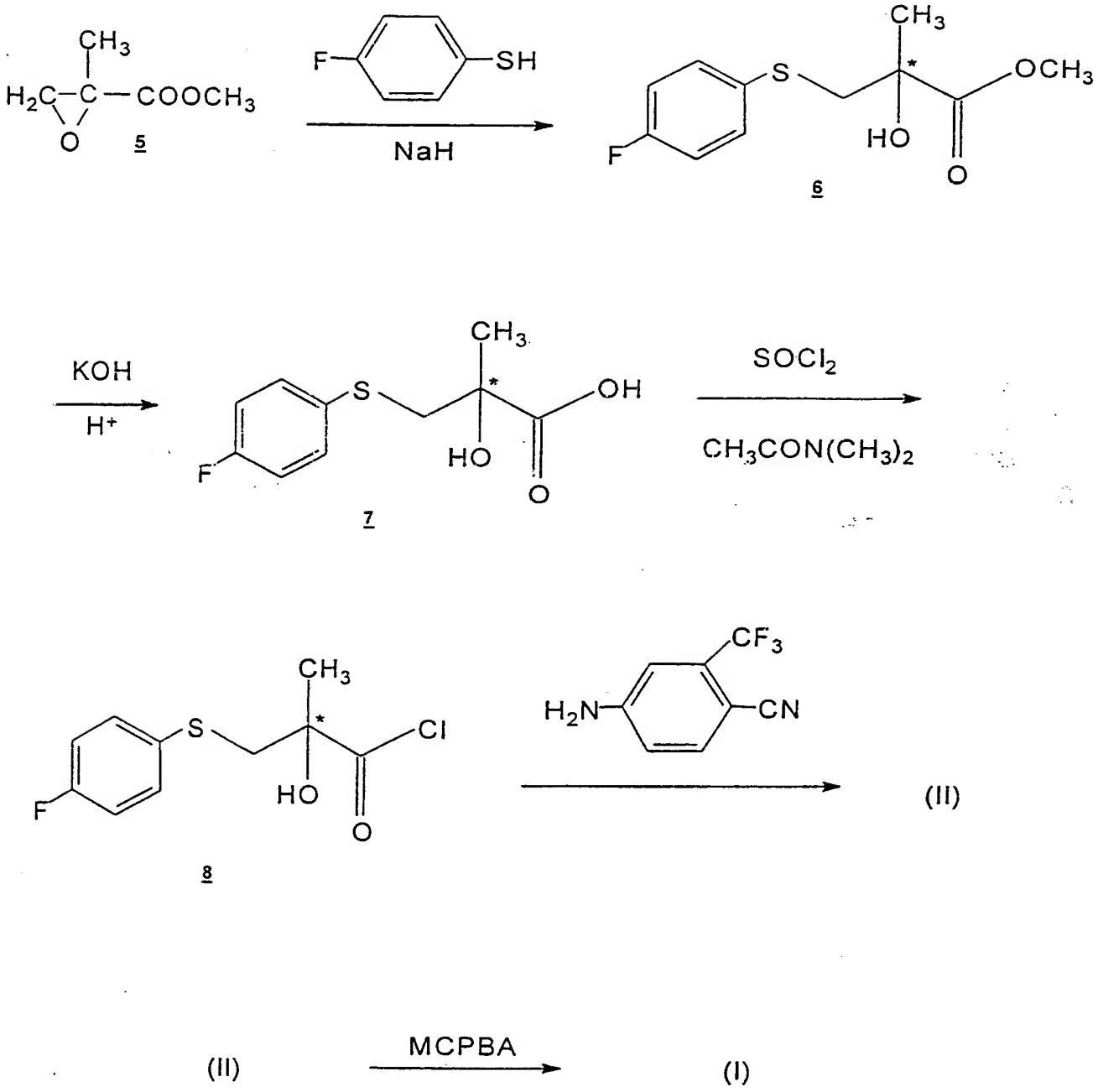
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Fig. 2

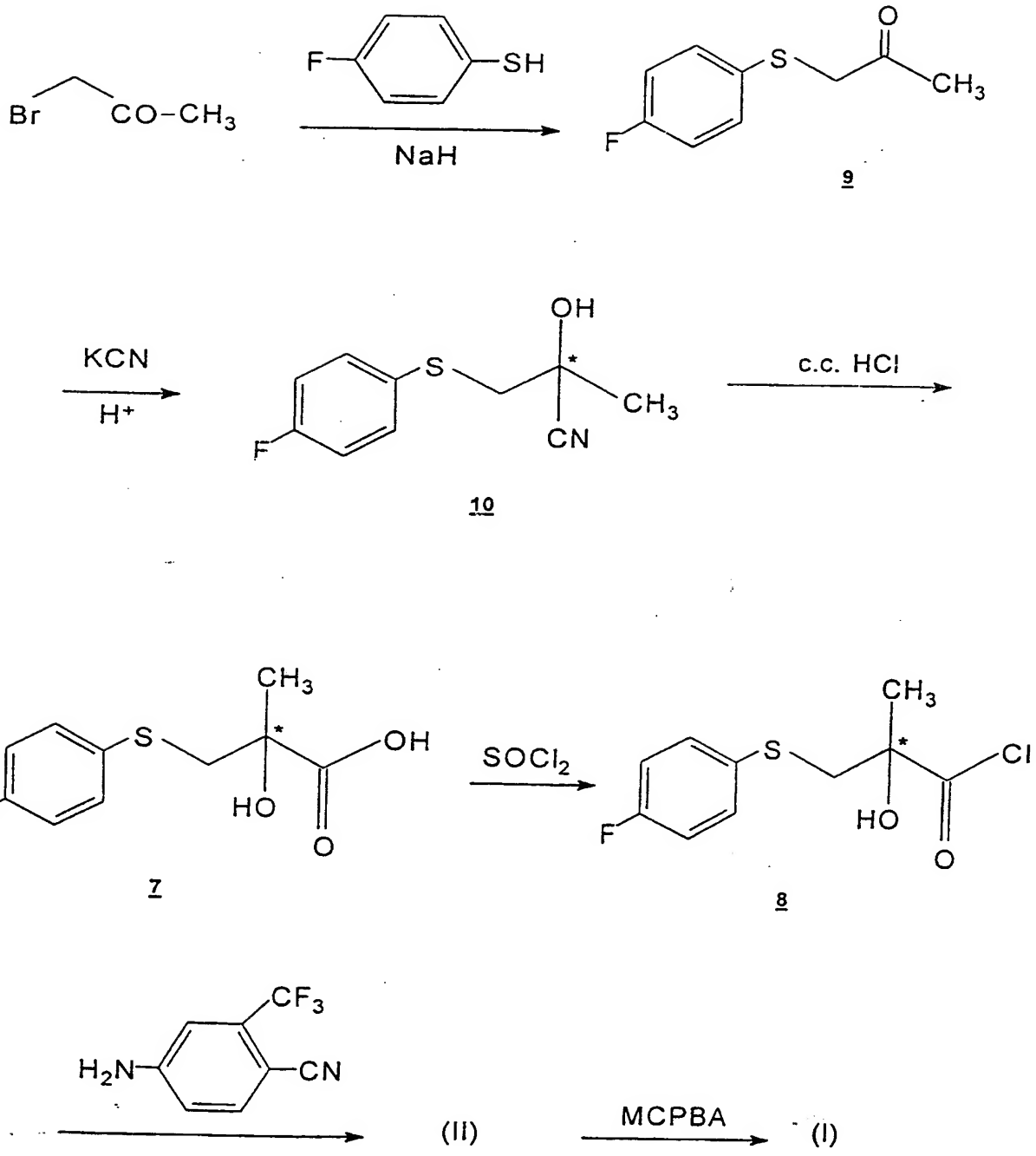
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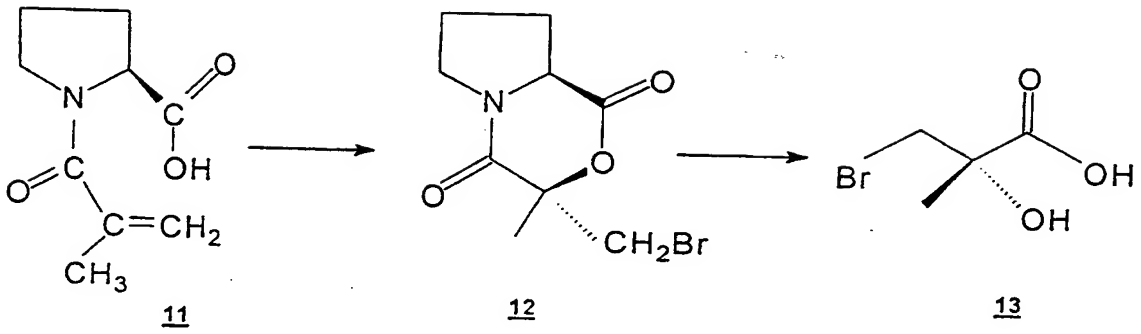
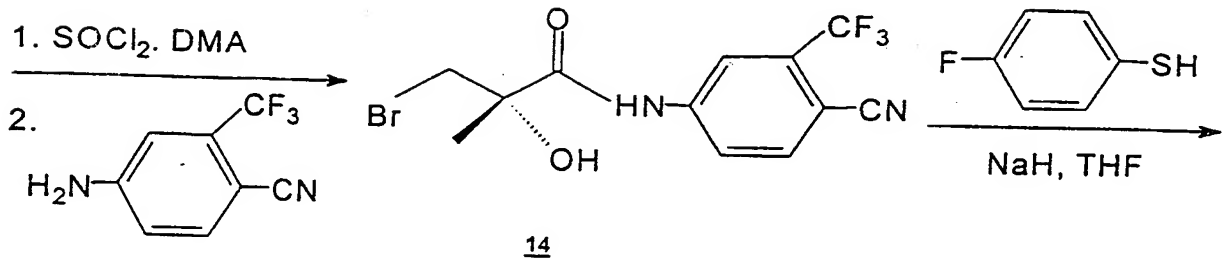
Fig. 3





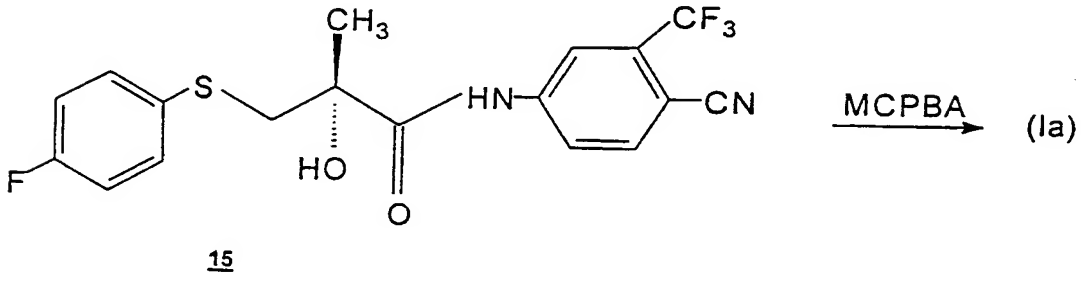
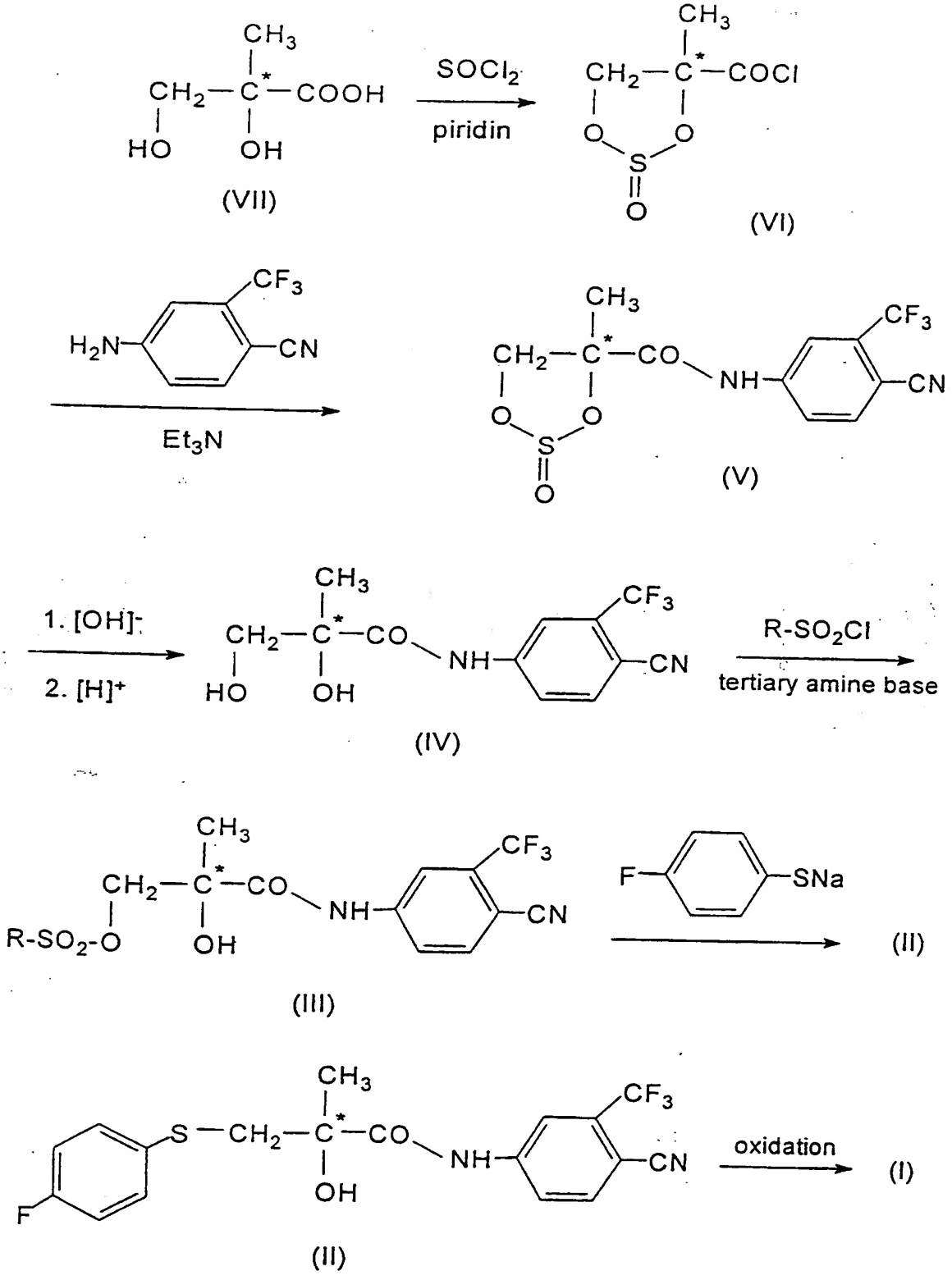


Fig. 4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CF3
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O O
S
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(V)
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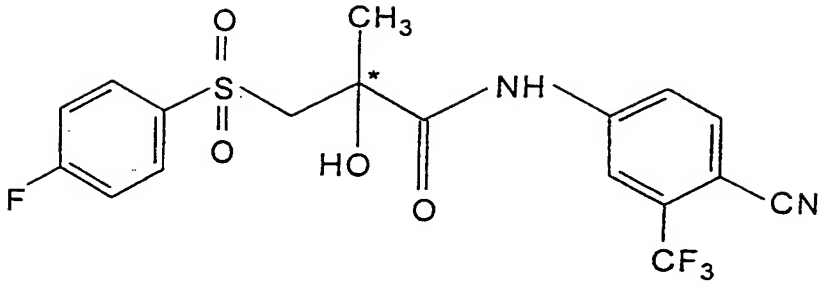
oxidation
(I)
(II)

Fig. 5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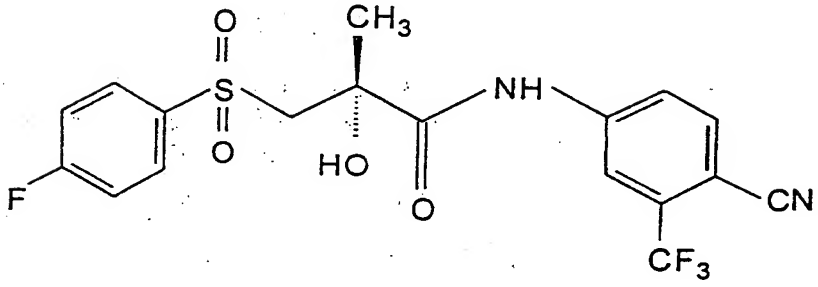
O
CH3
S
NH
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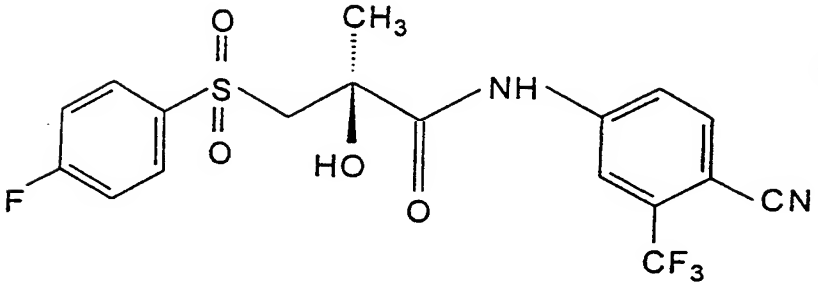
CF3

(Ia)


O
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CF3

(Ib)

Fig. 6

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/HU 00/00049

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D327/10 C07C253/30 C07C303/28 C07C309/66 C07C319/14
C07C323/60 C07C315/02 C07C317/46

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BEILSTEIN Data, WPI Data, EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 100 172 A (IMPERIAL CHEMICAL INDUSTRIES) 8 February 1984 (1984-02-08) cited in the application page 27, table, 8th entry claim 6 --- -/--	1

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 October 2000	27/10/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	English, R

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INTERNATIONAL SEARCH REPORT

Inter[illegible]nal Application No
PCT/HU 00/00049

C.(Continuation) DOCUMENTS CO[illegible]ERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	H. TUCKER, ET AL.: "Nonsteroidal antiandrogens. Synthesis and structure-activity relationships of 3-substituted derivatives of 2-hydroxypropionanilides" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 5, 1 May 1988 (1988-05-01), pages 954-959, XP000605264 American Chemical Society, Washington, DC, US ISSN: 0022-2623 cited in the application compound 40 ---	1
A	H. TUCKER, ET AL.: "Resolution of the nonsteroidal antiandrogen 4'-cyano-3-'(4-fluorophenyl)sulphonyl!-2-hydroxy-2-methyl-3'-(trifluoromethyl)-propionanilide and the determination of the absolute configuration of the active enantiomer" JOURNAL OF MEDICINAL CHEMISTRY, vol. 31, no. 4, 1 April 1988 (1988-04-01), pages 885-887, XP000605163 American Chemical Society, Washington, DC, US ISSN: 0022-2623 cited in the application the whole document -----	1

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INTERNATIONAL SEARCH REPORT

Interr al Application No
PCT/HU 00/00049

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